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# Seizure recurrence after a first generalized tonic–clonic seizure, in children, adolescents and young adults

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A sample of 78 patients (32 females and 46 males) who had a first unprovoked generalized tonic–clonic seizure between the age of 3 and 21 years was studied prospectively. Duration of follow-up was 2–10 years (mean 5.2 years). A second seizure occurred in 69.2% (54 of 78), most commonly (38 of 54, 70.37%) in the first three months after the first seizure. There were no significant differences in the total number of relapses among various aetiological groups. For idiopathic aetiology, seizure recurrence was significantly more common if the first seizure occurred during sleep (24 of 29, 82.75%) than in the waking state (5 of 13, 17.25%). The second seizure occurred in the same state, i.e. night sleep or awake in 72.2% (39 of 54) of patients. The presence of epileptiform patterns in the first two EEGs in the waking state or in sleep was significantly associated with a highly increased risk of seizure recurrence.

*Key words:* first generalized tonic–clonic seizure; predictors of seizure recurrence; epileptiform EEG patterns; epileptic syndromes.

## INTRODUCTION

Estimating the risk of recurrence after a first generalized tonic–clonic seizure (GTCS) was the subject of many reports[1–7] showing discrepant results. A recent meta-analysis[8] of 16 reports dedicated to this topic tried to explain the discrepancies among various authors by differences in the study methods and distribution of important prognostic factors.

This ongoing study provides our initial data obtained by a prospective assessment of the risk of recurrence after a first unprovoked GTCS in children, adolescents and young adults.

## METHODS

Children, adolescents and young adults referred to the Department of Neurology and Psychiatry for Children and Youth, in Belgrade, with the suspicion of their first GTCS, were thoroughly investigated in order to make a reliable diagnosis. A detailed history and neurological examinations were the basis for seizure classification[9]. Patients with an eye witness report of partial onset of their first GTCS and/or other postictal focal signs were not included. Also patients with obvious seizure-provoking factors, except for stress or partial sleep deprivation, have also been excluded.

All patients were first seen between 1 and 14 days after their seizure. The diagnosis of GTCS was based on the following criteria; (1) loss of consciousness from 1–30 minutes, (2) tonic phase, (3) clonic phase, (4) sphincter disturbance, (5) tongue biting, (6) fall, (7) injury due to fall, (8) postictal muscle soreness, sleep and confusion. Thus, a GTCS is considered to have definitely occurred if criteria 1–3 are present with any two of criteria 4–9[10].

Before the study, inter-rater reliability of diagnostic criteria was assessed by kappa statistics[11], and only patients whose diagnosis was agreed in discussion between both neurologists (ŽM and NJ) were included. The seizure aetiology was classified into id-

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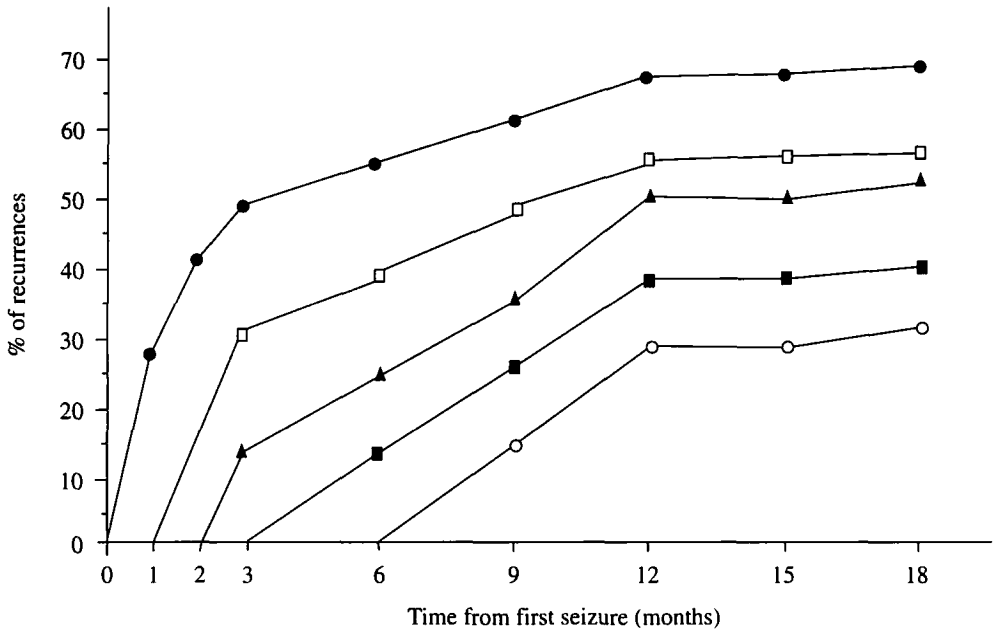


Fig. 1: Actuarial percentage recurrences after first seizure and after various intervals without seizures. □, seizure free after 1 month; ▲, seizure free after 2 months; ■, seizure free after 3 months; ○, seizure free after 6 months; ●, all patients.

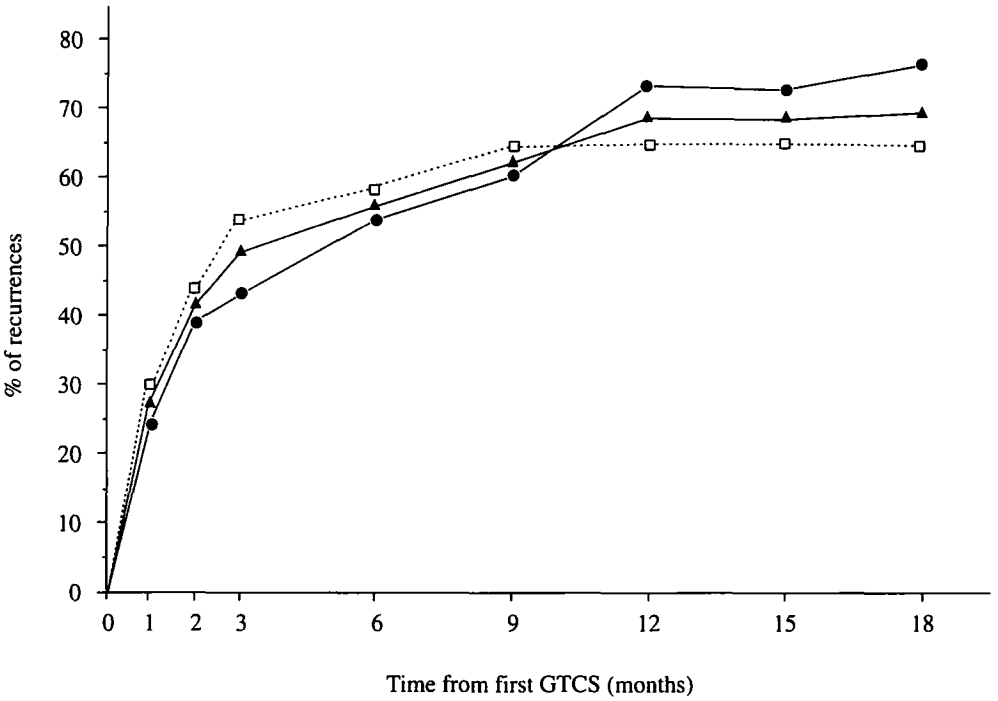


Fig. 2: Actuarial percentage recurrences after first GTCS by treatment status. ●, treated; □, untreated; ▲, all patients.

iopathic, cryptogenic or remote symptomatic[12]. The age span of patients at their first seizure was 3–21 years, the latter including the upper onset limit for idiopathic aetiology. Patients with acute symptomatic aetiology, i.e. febrile convulsions, immediate post-traumatic seizures, meningitis, encephalitis as well as with progressive neurological diseases and neonatal seizures were excluded.

Electroencephalograms (EEGs) were recorded after the first GTCS in intervals of 1 month for the first 3 months, and then once every 3 months. If the first awake tracing did not record epileptiform paroxysms, the EEG was performed during sleep on long-term monitoring or after sleep deprivation. Other ancillary investigations included blood chemistry in all patients and endocranial computerized tomography in 43.

The patients who were treated after a first GTCS were also included if all the above criteria were satisfied. The chi-square test was used to examine the difference in distributions of recurrence rates and times to recurrence for the various risk factors considered. The cumulative risks of recurrence were determined by life-table methods, with event defined as unprovoked seizure recurrence[13].

## RESULTS

The main features of our sample of 78 patients who satisfied all criteria for inclusion in this study are shown in Table 1 and their cumulative risk of seizure recurrence at different time intervals elapsed after first GTCS in Fig. 1. Evidently, the risk of recurrence was greatest during the first three months when a second seizure occurred in 38 of 54 (70.37%) of all recurrences. The recurrence type was GTCS in 36 of 54 (66.7%) patients, and in 18 (33.3%) patients other seizure types occurred (partial in 14 and myoclonic in 4).

The analysis showed that the age at first GTCS was not predictive of recurrence *per se*. When the time intervals preceding seizure recurrence were analyzed in relation to aetiology, patients in the symptomatic group tended to relapse earlier. Among 14 patients relapsing with partial seizures the aetiology was symptomatic in nine, kryptogenic in four and idiopathic in only one. However, the total number of relapsed patients among the three various aetiologic groups was not significantly different (see Table 2).

Table 1: Main characteristics of patients.

| | |
|---|---|
| Number of patients | 78 |
| Sex (M/F) | 46/32 |
| Age at first GTCS: | |
| Range | 3–21 years |
| Mean | 9.3 years |
| Number of patients with recurrent seizures | 54 (68.3%) |
| Interval between first GTCS and recurrence | 0.3–18 months |
| Follow-up period: | |
| Range | 2–10 years |
| Mean | 4.1 years |
| Seizure aetiology (number of patients): | |
| Idiopathic | 50 (64.1%) |
| Cryptogenic | 16 (20.5%) |
| Remote symptomatic | 12 (15.4%) |
| Treatment status after first GTCS: | |
| Number of untreated patients | 45 |
| Number of treated patients | 33 |

Table 2: Seizure recurrence related to aetiology.

| | Seizure | | Recurrence | | Total | |
|---|---|---|---|---|---|---|
| Aetiology | Yes | % | No | % | | % |
| Idiopathic | 32 | 41.0 | 18 | 23.1 | 50 | 64.1 |
| Cryptogenic | 12 | 15.4 | 4 | 5.1 | 16 | 20.5 |
| Symptomatic | 10 | 12.8 | 2 | 2.6 | 12 | 15.4 |
| Total | 54 | 69.2 | 24 | 30.8 | 78 | 100.0 |

$\chi^2 = 2.00$, $P > 0.05$.

Table 3: Epileptiform EEG patterns in first two EEGs related to the risk of recurrence.

| | Epileptiform EEG patterns | | |
|---|---|---|---|
| Seizure recurrence | Yes | No | Total |
| Yes | 51 | 3 | 54 |
| No | 14 | 10 | 24 |

$\chi^2 = 15.6$, $P < 0.001$.

Table 4: Types of epileptiform EEG related to recurrences.

| | Recurrences | |
|---|---|---|
| Interictal epileptiform EEG types | Yes | No |
| Bilateral rhythmic spike waves (3–4/second) | 20 | 2 |
| Bilateral irregular sharp and slow waves | 8 | 4 |
| Bilateral multiple spike waves | 6 | 0 |
| Focal spikes or sharp waves of non-Rolandic morphology | 12 | 2 |
| Focal sharp and slow waves | 4 | 3 |
| More than one of the above types | 19 | 0 |
| Focal centro-temporal spikes or sharp waves of Rolandic morphology | 1 | 3 |
| Total | 51 | 14 |

The first seizure occurred during sleep in 42 of 78 (53.8%) patients and during wakefulness in 36 (46.2%). The second seizure occurred in the same state in 39 (72.2%) of 54 patients and in a different state in 15 (27.8%) of a total of 54 patients with recurrences. The rate of recurrences was related to the physiological state (awake or asleep) at first GTCS and to the aetiology. This analysis showed that the recurrences were more frequent when the first GTCS occurred during sleep, but these differences for the overall sample did not reach statistical significance. However, the risk of recurrence for the idiopathic aetiological group was significantly greater if the first seizure occurred during sleep. Thus, the relapse occurred in 24 of 29 patients with the first seizure occurring whilst asleep and in only 8 of 21 patients with the first seizure occurring when awake ($\chi^2 = 17.56$, $P < 0.001$).

The presence of epileptiform EEG patterns in the first two EEGs (including prolonged monitoring and/or sleep after sleep deprivation in 22 patients) was predictive for seizure recurrence (see Table 3). As to the type of epileptic EEG discharges and their predictive value (see Table 4), the number of patients is small for definite conclusions. However, only bilateral multiple spike waves or the coexistence of several types of epileptiform patterns in the same EEG have been associated invariably with the recurrence.

The percentage of recurrences after the first GTCS was related to treatment status (see Fig. 2). No significant differences between treated and untreated groups emerged. In spite of patient and parent counselling, the initial compliance with treatment was low. Many

parents choose to give the treatment even when informed about the favourable or excellent outcome, such as in patients with a normal EEG or in BPE with Rolandic spikes. On the other hand, the treatment was not initiated in 11 patients showing several interictal epileptiform EEG patterns associated with a very high risk of seizure recurrence (Table 4).

## DISCUSSION

Due to several differences in the age and clinical features of the patient sample, the results of the present study are not strictly comparable with other studies estimating the risk of seizure recurrence[1–8]. Since the present study included young patients after a first GTCS in clinical situations, it was not expected to be representative for the population as a whole.

However, our results are in agreement with the data of large-scale population studies[5,7] showing that the highest seizure recurrence rates are observed in the first six months after a first GTCS. Compared with other studies[1–8], the recurrence rate of the present sample (54 of 78, 69.2% of patients) is among the higher values in a wide range from the lowest 23%[2] to the highest 71%[3]. Our finding is probably due to the exclusion of patients with acute symptomatic aetiology where a lower recurrence rate (40% by 12 months) was reported[4]. We also included young patients with remote symptomatic and idiopathic seizures having higher recurrence rates at an early interval after first GTCS[14]. As reported in a large population study, patients under the age of 16 years had a risk of recurrence of 83% by 36 months, and in a follow-up study the risk of recurrence was 68% by 2.5 years[5]. The great majority of recurrences (85%) in this large study[5] as well as in the present report occurred within the first 6 months.

In this study, the main predictor of seizure recurrences after the first GTCS between the ages of 3 and 21 years was the presence of epileptiform EEG discharges. This was apparent for all aetiological groups while Shinnar *et al*[14] found that in children with various seizure types a higher recurrence risk was associated with an idiopathic aetiology and with remote symptomatic seizure aetiology if followed by partial seizures. Due to very high recurrence rates in all aetiological groups, we could not statistically prove the eventual differences among them.

The finding of epileptic discharges in adult patients with untreated idiopathic first seizure was associated with a risk of recurrence of 83% versus 41% or 12% in patients with either non-epileptiform abnormalities or with normal EEGs[15]. A recent study[16] included EEGs with records during both the waking and sleep state in 48% of 321 children (age range was not given) with various types of first unprovoked seizure. The difference in recurrence rate between patients with epileptiform EEG abnormalities (59%) and those with non-epileptiform abnormalities (35%) was statistically significant ($P = 0.05$), i.e. at a lower level than in the present study where all patients without epileptiform abnormalities when awake were given a sleep EEG record.

Although the numbers are small for statistical analysis, the highest predictive value should be ascribed to the presence of multiple epileptiform EEG patterns (Table 4). The types of epileptiform EEG patterns in our patients gave some early clues to the underlying epileptic syndrome[17] which would become apparent after recurrence. Therefore the decision to start treatment after a first GTCS in patients aged 3–21 years should take into account the morphology of EEG discharges apparent before recurrence. The bilateral multiple spike waves in six of our patients were apparent after their first GTCS. In four of them, they predated the recurrence of other (myoclonic) seizures. Although GTCS predating myoclonic jerks is a rare presentation of juvenile myoclonic epilepsy (JME)[18,19], the reverse order of seizure types being much more frequent, one should be aware of this possibility after a first GTCS and a finding of typical EEG paroxysms. These data may enable the diagnosis of JME, the syndrome in which the seizure control requires a long-term and rational antiepileptic drug (AED) treatment[18,19].

Our results have not confirmed other reports of significant reduction of seizure recurrence associated with the intake of AEDs after the first GTCS[20]. A low compliance with treatment might have diminished the possible treatment effects on seizure recurrence rate in our patients. Furthermore, this situation made our patients similar to untreated patients which suggested that the question of early treatment effect should be examined in other prospective controlled studies. However, the possibility that treatment status may have altered our results seems unlikely in the light of a very high seizure recurrence which was irrespective of treatment option.

The therapeutic option after first GTCS does not seem to affect the long-term prognosis of epilepsy[20]. Conversely, our results suggest that the treatment decision should be individualized on the basis of early EEG and clinical features of the eventual age-related epileptic syndromes[17] that can become apparent during follow-up. In patients lacking such 'syndromic' features, the identification of all eventual predictors of recurrence and/or prognosis in large-scale epidemiological studies might be useful for making decisions to start or defer treatment for preventing seizure recurrences[20].

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